Statements under 37 C.F.R. §1.173(c)

The following statements are made pursuant to the requirements of 37 C.F.R. §1.173(c). Patent claims 1-4 have been cancelled without prejudice toward the continuation of prosecution in a continuing application. Added claims 5-176 and 178-209 have also been cancelled without prejudice. Claims 177 and 210-214 are the only claims now pending in the case.

Pursuant to 37 C.F.R. §1.173(c), the following is an explanation of the support in the disclosure of the patent for the changes made to the claims by the present amendment.

Claims 210 and 211 have been amended to change "obtained from DNA encoding a monoclonal antibody …" to read "obtained by genetically engineering the DNA encoding a monoclonal antibody … ." Furthermore, claim 214 has been amended to change "the DNA of said selected monoclonal antibody …" to read "the DNA encoding said selected monoclonal antibody … ."

The concept of these changes is supported at column 10, lines 1-3, of the present specification where it states:

> The present invention uses genetically-engineered antibodies obtained from such selected antibodies ….

Language in a claim complies with the written description requirement of 35 USC 112 when it is supported through implicit or inherent disclosure. See MPEP 2163, Written Description Guidelines, where it states at section I.B.:

> While there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure.

That the genetically-engineered antibodies are obtained by genetically engineering the DNA encoding the selected monoclonal antibodies is implicit or inherent in the above-quoted portion of the present specification at column 10, lines 1-3. Thus, this language not only clarifies the claims, but is also fully supported by the specification.

The language at the top of column 10, lines 1-5, about genetically engineering a selected antibody clearly means genetically engineering a selected monoclonal antibody as the antibodies referred to in the previous two paragraphs were all monoclonal antibodies. For example, in the paragraph starting at column 9, line 33, the specification speaks of the availability of monoclonal antibodies which bind to a specific antigen and the isolation of those antibodies by "appropriate selection" (column 9, lines 33-41). Note also reference to "such monoclonal antibodies, when properly selected, …" at column 9, lines 41-42. Note also the sentence at column 9, lines 45-48, which reads:

> In addition, the use of engineered monoclonal antibodies … can be used in the present invention.

Clearly, the "genetically engineered antibodies" specified at column 10, line 1-2, refers back to the "engineered monoclonal antibodies" specified at column 9, lines 45-46, which have

been "properly selected" as specified at column 9, lines 41-42.

Furthermore, there is no other way to "genetically engineer" a monoclonal antibody than to engineer the DNA encoding the monoclonal antibody, as that is the definition of "genetic." Elsewhere in the specification, such as at column 11, in the paragraph beginning at line 33, there is explicit disclosure of the method of production of monoclonal antibodies by means of hybridoma technology. When one is in possession of the hybridoma producing a monoclonal antibody, one is in possession of the DNA encoding that monoclonal antibody. Furthermore, there is explicit disclosure of the use of the DNA encoding a monoclonal antibody, such as at column 5, lines 56-58, which states:

> The antigen binding site of an antibody can be determined from the DNA sequence of the respective CFR fragments.

Thus, the concept of antibody manipulation by means of the DNA encoding it is present in the specification and supports the interpretation that "genetically-engineered," as used at the top of column 10, means that the DNA encoding the monoclonal antibody is engineered.

Additionally, as stated in MPEP 2164.05(a):

> The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94

(Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

It was well known as of the effective filing date of the present application that the genetic engineering of monoclonal antibodies involves the engineering of the DNA encoding the monoclonal antibodies. Furthermore, the techniques for doing so were also well known as of the effective filing date of the present application. Note, for example, the references cited in the present specification as teaching "[r]ecent advances in antibody engineering technology" (column 16, lines 27-33). See also the reference cited at column 2, lines 62-64, and column 6, lines 7-15. Submitted herewith are copies of the following publications referred to at these sections and incorporated by reference into the present specification (column 16, lines 38-44):

Haber, "Engineered Antibodies as Pharmacological Tools," *Immunological Reviews*, 130:189-212 (1992).

Pluckthun, "Mono- and Bivalent Antibody Fragments Produced in Escherichia coli: Engineering, Folding and Antigen Binding," *Immunological Reviews* 130:151-188 (1992).

Travis, "Putting antibodies to work inside cells," *Science* 261:1114 (1993).

Marasco et A, "Design, intracellular expression, and activity of a human anti-human immunodeficiency virus type 1 gp120 single-chain antibody" *Proc. Natl. Acad. Sci. USA*, 90:7889-7893 (1993).

Haber deals with engineered antibodies (see title) and recognizes that recombinant DNA techniques are used to do

so (see, for example, page 196, first two paragraphs). In Pluckthun, see, for example, the second paragraph of the introduction, which speaks of the known ability to clone antibody genes using PCR of consensus DNA sequences. Note also the skill of the art demonstrated in the Marasco publication.

Accordingly, those of ordinary skill in the art reading the present specification and possessing the skill in the art of a person of ordinary skill as of the effective filing date of the present application would understand that the reference to genetically engineered antibodies obtained from selected monoclonal antibodies, as disclosed at columns 9 and 10 of the present specification, inherently or implicitly means that the genetically engineered antibodies are obtained by genetically engineering the DNA encoding the selected monoclonal antibodies and this new language in claims 210, 211 and 214 is accordingly not new matter as it is supported by subject matter inherently or implicitly present in the specification as filed, particularly in light of the state of the art presumed to be within the knowledge of a person of ordinary skill in the art.

REMARKS

Claims 177 and 210-214 presently appear in this case. No claims have been allowed. The official action of June 19, 2008, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a therapeutic composition that comprises a pharmaceutical formulation of a pharmaceutically acceptable carrier and a human or genetically-engineered monoclonal antibody or antibody binding fragment thereof. The antibody is one that either inhibits aggregation of β-amyloid or maintains the solubility of soluble β-amyloid. The genetically-engineered antibody is obtained from DNA encoding a monoclonal antibody that either recognizes an epitope within residues 1-28 of β-amyloid or is obtainable using a peptide consisting of residues 1-28 of β-amyloid as an immunogen. The human monoclonal antibody must be one that is obtainable using a peptide consisting of residues 1-28 of β-amyloid as an immunogen. The invention also relates to a method for making such a pharmaceutical formulation by first selecting the monoclonal antibody and then genetically engineering it prior to incorporating it into a pharmaceutical formulation.

Copy of Claims in Conventional Amended Format

MPEP §1453.V.D. states with respect to the amendment of new claims:

> Although the presentation of the amended claim does not contain any indication of what is changed from the previous version of the claim, applicant must point out what is changed in the "Remarks" portion of the amendment.

Claims 177, 212 and 213 have not been amended by the present amendment. All of claims 210, 211 and 214 are previously presented new claims in the sense that they were not present in the patent as issued and are being amended by the present amendment. So that the examiner can see how the claims are being amended from the previous version of these claims, the following is a recitation of all of the pending claims, including the three amended claims, shown in the conventional amended format:

1-176 (Cancelled).

177 (Previously Presented). The therapeutic composition of claim 210 or 211, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

178-209 (Cancelled).

210 (Currently Amended). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid, or

(b) a fragment of the genetically-engineered antibody of (a) that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid,

wherein said genetically-engineered antibody is obtained ~~from~~ by genetically engineering the DNA encoding a monoclonal antibody that

(i) inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid and

(ii) is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen or recognizes an epitope within residues 1-28 of beta-amyloid.

211 (Currently Amended). The therapeutic composition of claim 210, wherein said genetically-engineered antibody of (2)(a) inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid, or said fragment of (2)(b) inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid, and said genetically-engineered antibody of (2)(a) is obtained ~~from~~ by genetically engineering the DNA encoding a monoclonal antibody that inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid and said monoclonal antibody is obtainable using a peptide consisting of residues 1-28 of human beta-amyloid as

an immunogen or recognizes an epitope within residues 1-28 of human beta-amyloid.

212 (Previously Presented). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a human monoclonal antibody that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid, or

(b) a fragment of the human monoclonal antibody of (a) that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid,

wherein said human monoclonal antibody is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen.

213 (Previously Presented). The therapeutic composition of claim 212, wherein said human monoclonal antibody of (2)(a) inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid, or said fragment of (2)(b) inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid, and wherein said human monoclonal antibody of (a) is obtainable using a peptide consisting of residues 1-28 of human beta-amyloid as an immunogen.

214 (Currently Amended). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered

antibody that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid, or (b) a fragment of the genetically-engineered antibody of (a), which fragment inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid, said method comprising:

selecting a monoclonal antibody that

(i) inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid, and

(ii) is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen or recognizes an epitope within residues 1-28 of beta-amyloid;

genetically engineering the DNA ~~of~~ encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid, or a fragment of a genetically engineered antibody, which fragment inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

Applicant's Statement of Substance of Interview

The interview, graciously granted, among Examiner Gregory Emch, Supervisory Examiner Elizabeth Kemmerer, the Quality Assurance and Reissue Specialist Robert Wax and the undersigned and Harris Pitlick, representing the applicant, on

October 8, 2008, is hereby gratefully acknowledged. The following is a summary of what transpired at the interview.

The first issue discussed was the new matter/anticipation problem. We (applicant's attorneys) explained that from the examiner's treatment of claim 214, it was apparent that the examiners agreed that if the claims were written so as not read on a monoclonal antibody, i.e., to require selection of the antibody first and then genetic engineering of the selected antibody, this would obviate the anticipation rejections other than over Anderson. The examiners were informed that we understood their interpretation that the language previously submitted did not obviate the anticipation rejection (although we did not necessarily agree with that interpretation) and we suggested amending the claims to specify "genetically engineered antibody obtained by genetic engineering of the DNA encoding a monoclonal antibody …." After discussing this language strictly from the point of view of anticipation, the examiners tentatively agreed that, disregarding for the moment any new matter or other 35 USC 112 problems with this language, it should obviate the anticipation rejections based on monoclonal antibodies *per se*.

As to the new matter issue, we explained that the language at the top of column 10, lines 1-5, of the present specification about genetically engineering a selected antibody clearly meant genetically engineering a selected monoclonal antibody as this language was used in the previous

two paragraphs (for example, in the paragraph starting at column 9, line 33). We further pointed out that there is no other way to "genetically engineer" an antibody than to engineer the DNA encoding the antibody, as that is the definition of "genetic." The examiners stated that their problem was that the specification did not have any support for DNA and that there was no disclosure of DNA. We pointed out that the specification disclosed monoclonal antibodies and that ones of ordinary skill in the art certainly were in possession of the DNA encoding the monoclonal antibodies if they were in possession of the hybridomas from which the monoclonal antibodies were obtained. We also explained that this was part of the prior art. We pointed out that the Haber reference, for example, is described in the specification for preparing antibodies and that the specification indicates that the title of this reference has to do with genetically engineering antibodies. We stated that the references incorporated in the present specification disclosed how one can determine the DNA of a given monoclonal antibody so that one could humanize it or make a single chain antibody, etc.

The examiners agreed that written description was not necessary if this subject matter was described in the prior art and they said that they would review the Haber reference. The examiners tentatively indicated that if, as of the filing date of the present application, it would not have been undue experimentation to obtain the DNA encoding a monoclonal antibody and manipulate it, then they would tend to

agree that the proposed claim language would not be new matter or subject to other §112 problems.

We next discussed the issue as to whether the Anderson reference could be antedated. We showed the examiners the case, which will be discussed below, that explicitly said that the sending of a specification from abroad to a U.S. attorney establishes a date of conception of the invention in the United States. The examiners said that they had not been aware of any case law on this issue and that if this is the law, then they would simply withdraw that rejection. The rejection was based only on the MPEP that they quoted, which they agreed was somewhat ambiguous. I asked Examiner Emch if he had already substantively considered the evidence presented with the declaration and he said that he had considered it and that if the legal objection is withdrawn he agreed that it established conception and diligence. This would remove Anderson as a reference.

We next discussed the Gaskin rejection. We discussed what was necessary for the examiner to make an anticipation rejection based on inherency. The examiners agreed with us that the MPEP indicated that for an examiner to make an inherency argument, the examiner must have reasonable grounds to conclude that the specified properties are **necessarily** present in the prior art substance. In view of this standard, they said that if we submitted a declaration that showed that it would not be reasonable to conclude that the antibody would necessarily be produced using Aβ 1-28 as an

immunogen, they would have to withdraw the rejection. Such a declaration is being submitted herewith and will be discussed below.

Finally, the obviousness rejections were discussed. We pointed out that, with Anderson being antedated, this left only Becker as allegedly motivating the therapeutic use of the antibodies of the primary references. We explained that in order for there to be motivation to use those antibodies therapeutically, the motivation must be from something that is in the prior art. Thus, if Becker states that one must select from the universe of anti-Aβ antibodies only those that bind to the β-sheet form of Aβ, but not to the α-coil form, then there must be some reason to believe that the antibodies of the primary references fit this description. If there is no reasonable reason to believe that they will necessarily bind to the β-sheet form, then there would be no motivation to try to use such antibodies therapeutically, and thus have a reason to subject them to genetic engineering. We explained our consternation that the examiner stated that there is nothing about β-sheets in the claim, so we should not be arguing it. We explained that, before it would be obvious to use the antibodies of the primary references therapeutically for the purpose of Becker, the examiner must establish a *prima facie* case that the antibodies of the primary references will selectively bind to the β-sheet form of Aβ. The examiner stated that he would reconsider the rejection in light of our arguments when we submit our response.

While no firm agreements were reached at the interview, progress was made in advancing prosecution of this case. The arguments presented at the interview will also be fleshed out in the discussion of the specific rejections hereinbelow.

Formalities

It is noted that the examiner has reminded applicant and applicant acknowledges the continuing obligation under 37 CFR 1.178(b) to timely apprise the Office of any prior or concurrent proceeding in which patent no. 5,688,651 is or was involved, and the continuing obligation under 37 CFR 1.56, to timely apprise the Office of any information that is material to patentability of the claims under consideration in the reissue application.

The application has been objected to under 37 CFR 1.172(a) as lacking the written consent of all assignees owning an undivided interest in the patent. A proper assent of the assignee in compliance with 37 CFR 1.172 and 3.73 has been required. This objection is respectfully traversed.

The examiner has apparently overlooked the consent of assignee that was filed on May 25, 2001. A copy of this consent, as downloaded from the PTO Public PAIR website, is attached hereto. Note that while it was indexed as a miscellaneous incoming letter, it is clearly an executed written consent of assignee. The consent refers to the showing of ownership per 37 CFR 3.73(b) previously filed. A

copy of the 3.73(b) statement filed on November 16, 1999, as downloaded from the PTO Public PAIR database, is also attached hereto. Reconsideration and withdrawal of this objection is therefore respectfully urged.

The examiner states that the reissue declaration filed with this application is defective because the amendment to the claims dated March 19, 2007, is not supported by a proper supplemental reissue declaration under 37 CFR 1.175. Accordingly, a supplemental reissue declaration under 37 CFR 1.175(b)(1) must be received before the reissue application can be allowed.

Furthermore, claims 177 and 210-214 have been rejected as being based upon a defective reissue declaration for the reasons discussed in the previous paragraph. The examiner states that receipt of an appropriate supplemental declaration under 37 CFR 1.175(b)(1) will overcome this rejection.

Attached hereto is a supplemental declaration under 37 CFR 1.175. This is in compliance with the examiner's requirement and obviates the rejection.

The examiner notes that more than one reissue application has been filed for reissue of U.S. patent 5,688,651. The examiner has objected to the present application under 37 CFR 1.177(a), which requires that all multiple reissue applications resulting from a single patent must include as the first sentence a cross-reference to the other reissue application(s).

The present specification has now been amended to insert the notice of multiple reissue applications as the first sentence thereof, in compliance with 37 CFR 1.177(a). Reconsideration and withdrawal of this objection is therefore respectfully urged.

Sufficiency of Declaration under 37 CFR 1.131

The examiner states that the declaration under 37 CFR 1.131 and the supplemental declarations of Kohn, Hirsch and Browdy filed on March 19, 2007, are insufficient to establish that conception, coupled with reasonable diligence, was established in the United States from a date immediately prior to November 22, 1994, to the filing date of December 6, 1994. Therefore, the examiner states that the declarations are insufficient to overcome the rejection of claims 177 and 210-213 under 35 U.S.C. 102(e), as being anticipated by Anderson. The examiner states that the content of the declarations is not challenged. However, the examiner states that the fact that conception was communicated to the United States prior to November 22, 1994, does not establish that conception was in the United States. The examiner states that conception and diligence as well as reduction to practice occurred in Israel before the invention was communicated to the United States. This holding of insufficiency is respectfully traversed.

Applicant respectfully submits that the examiner is misinterpreting MPEP 715. Applicant is not relying upon

conception in a WTO member country prior to January 1, 1996. Applicant is relying on conception in the United States. Similarly, applicant is relying on acts of diligence that took place in the United States.

That the communication of a conception to the United States as a draft patent application after the invention was originally conceived abroad is sufficient to establish conception in the United States, is well established by the case law. Submitted herewith for the examiner's consideration is *Ex Parte Hachiken*, 223 USPQ 879, 880 (Bd. Pat. App. 1984), stating that "the date of a draft application originating in a foreign country is introduced into this country by way of counsel may be taken as the date of conception of the invention in this country." As that case involved an invention that was originally conceived in a country that is now a WTO member country, before January 1, 1996, it is on all fours with the present situation. In view of the current state of the law as evidenced by the *Hachiken* case, the holding of insufficiency of the declaration under 37 CFR 1.131 must be withdrawn. Acceptance of this declaration as establishing a date of invention prior to November 22, 1994, thereby antedating the Anderson patent is therefore respectfully urged.

New Matter Rejection

Claims 177, 210, 211 and 214 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply

with the written description requirement. The examiner states that this is a new matter rejection. The examiner states that he could not find support in the disclosure as filed for the limitation "wherein said genetically-engineered antibody is obtained from DNA encoding a monoclonal antibody." The examiner has invited applicant to identify sufficient written support in the original specification for the language indicated above. The examiner states that the passage at column 10, lines 1-3, does not provide support for this language since an antibody, as disclosed in the specification, is an amino acid molecule that is structurally and functionally distinct from DNA, a nucleic acid molecule. This rejection is respectfully traversed.

The examiner's attention is respectfully invited to the statements under 37 CFR §1.173(c) made hereinabove, explaining in great detail why the present language of the claims, which now reads "obtained by genetically-engineering the DNA encoding a monoclonal antibody" or, in claim 214 "the DNA encoding said selected monoclonal antibody," finds support in the disclosure of the specification as originally filed, which support may be either explicit, inherent or implicit. Reference to the DNA sequence of monoclonal antibodies is explicitly present in the present specification at column 5, lines 56-58. Furthermore, it was well known as of the effective filing date of the present application that the genetic-engineering of monoclonal antibodies must involve the engineering of the DNA encoding the monoclonal antibodies, and

techniques for doing so were also well known as of the effective filing date of the present application. The statements under 37 CFR §1.173(c) hereinabove discuss the various prior art publications incorporated by reference into the present specification and how they establish that engineering the DNA encoding monoclonal antibodies was within the skill of the art as of the effective filing date of the present application. Those of ordinary skill in the art reading the present specification would understand that there is no other way to "genetically-engineer" an antibody than to engineer the DNA encoding the antibody as that is the definition of "genetic."

In the above discussed interview, the examiners agreed that written description was not necessary if the subject matter was described in the prior art. The above discussion in the statements under 37 CFR §1.173(c) establishes that it would not involve undue experimentation to obtain the DNA encoding a monoclonal antibody and manipulate it. Accordingly, those of ordinary skill in the art reading the present specification and possessing the skill of a person of ordinary skill in the art as of the effective filing date of the present application would understand that the reference to "genetically-engineered antibodies obtained from selected monoclonal antibodies," as disclosed at columns 9 and 10 of the present specification, inherently or implicitly means that the genetically engineered antibodies are obtained by genetically-engineering the DNA encoding the selected

monoclonal antibodies and this language is not new matter as it is supported by subject matter inherently or implicitly present in the specification as filed. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Anticipation Rejections over Bickel, Stern, Walker and Suzuki

Claims 210 and 211 have been rejected under 35 U.S.C. 102(b), as being anticipated by Bickel as further evidenced by Solomon. The examiner interprets the claim language "wherein said genetically-engineered antibody is obtained from DNA encoding a monoclonal antibody" as not defining over a standard monoclonal antibody. The examiner states that a monoclonal antibody *is* a genetically-engineered antibody that is obtained from DNA encoding a monoclonal antibody. This rejection s respectfully traversed.

The antibodies of the present invention, as claimed in claims 210 and 211, are not monoclonal antibodies but are genetically-engineered antibodies. First, one must select an appropriate monoclonal antibody and then one must genetically-engineer the DNA encoding that monoclonal antibody so as to produce something different from the original monoclonal antibody. That an antibody produced in such a manner distinguishes over a "monoclonal antibody" as disclosed in the references is evident from the fact that claim 214 was not included in this rejection.

In order to avoid any possibility of interpreting the definition of "genetically-engineered antibody" as set

forth in claims 210 and 211 so as to encompass a monoclonal antibody, claims 210 and 211 have now been amended to specify that the genetically-engineered antibody "is obtained by genetically-engineering the DNA encoding a monoclonal antibody." The monoclonal antibody of Bickel is not obtained by genetically-engineering the DNA encoding a monoclonal antibody. It is obtained by making a hybridoma of an antibody-producing cell and a cancer cell. The present definition of a genetically engineered antibody in claims 210 and 211 cannot read on the monoclonal antibody of Bickel.

The language being presented in claims 210 and 211 was discussed with the examiners in the interview and the examiners tentatively agreed at the interview that, disregarding for the moment any new matter or other 35 U.S.C. 112 issues, this language would distinguish over simple monoclonal antibodies such as those of Bickel, Stern, Walker, Suzuki and Gaskin. It has been shown hereinabove that this language does not comprise new matter. As the monoclonal antibodies of Bickel, as well as Stern, Walker, Suzuki or Gaskin, are not obtained by genetically-engineering the DNA encoding a monoclonal antibody, the present claims cannot be anticipated by Bickel, Stern, Walker, Suzuki or Gaskin. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 210 and 211 have been rejected under 35 U.S.C. 102(b) as being anticipated by Stern as further

evidenced by Solomon. This rejection is respectfully traversed.

The examiner's reasoning here is exactly the same as that discussed above with respect to the rejection over Bickel as further evidenced by Solomon. As with Bickel, Stern teaches only a monoclonal antibody and not a genetically-engineered antibody as defined in presently amended claims 210 and 211. Accordingly, this rejection must fall for the same reasons as discussed hereinabove with respect to the rejection over Bickel. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

Claims 210 and 211 have been rejected under 35 U.S.C. 102(a) as being anticipated by Walker as further evidenced by Solomon. This rejection is respectfully traversed.

Walker, like Bickel and Stern discussed hereinabove, is directed to a monoclonal antibody, not a genetically-engineered antibody as defined in claims 210 and 211. Accordingly, this rejection must fall for the same reasons as discussed hereinabove with respect to the rejections over Bickel and Stern. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 210 and 211 have been rejected under 35 U.S.C. 102(e) as being anticipated by Suzuki as evidenced by Solomon. This rejection is respectfully traversed.

As with Stern, Bickel and Walker, Suzuki teaches only a monoclonal antibody, not a genetically-engineered

antibody as presently defined in claims 210 and 211. Accordingly, this rejection must fall for the same reasons as discussed above with respect to the rejections over Stern, Bickel and Walker. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Anticipation rejection over Anderson

Claims 177 and 210-213 have been rejected under 35 U.S.C. 102(e), as being anticipated by Anderson as evidenced by Solomon. This rejection is respectfully traversed.

Applicant hereby incorporates by reference all of the arguments in previous amendments as to why claims 177 and 210-213 would not be anticipated by Anderson even if Anderson were available as a reference. However, it is not necessary to again review such arguments in view of the fact that the declaration under 37 CFR 1.131 and supporting materials previously submitted establish that the present application antedates Anderson and therefore Anderson is not available as a reference. It has been explained hereinabove why the case law requires that the conception communicated to the United States by means of a patent application forwarded to a U.S. attorney from a foreign country does indeed establish a date of conception in the United States. As such communication is a legally sufficient conception and as the examiner has indicated in the interview that, if the communication and diligence are considered to be conception and diligence in the United States, the evidence would be sufficient to establish a

date of invention prior to November 22, 1994. Accordingly, Anderson has been antedated. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Anticipation rejection over Gaskin

Claims 210-213 have been rejected under 35 U.S.C. 102(b) as being anticipated by Gaskin as evidenced by Solomon. With respect to claims 210 and 211, the examiner asserts that the definition of genetically-engineered antibody as set forth in these claims does not distinguish over a monoclonal antibody and that Gaskin establishes that the antibody recognizes an epitope within residues 1-28 of β-amyloid. With respect to claims 212 and 213, the examiner states that the antibodies of Gaskin are human monoclonal antibodies and that they are obtainable using a peptide consisting of residues 1-28 of β-amyloid as an immunogen. The examiner states that the fact that the antibody may cross-react with other portions of Aβ or that other portions of a peptide molecule may contribute to epitope stability is immaterial where the antibody is already evidenced to bind the requisite epitope. This rejection is respectfully traversed.

With respect to claims 210 and 211, this rejection must fall for the same reasons as discussed above with respect to the Bickel, Stern, Walker and Suzuki rejections. Gaskin teaches only a monoclonal antibody and not a genetically-engineered monoclonal antibody as defined in presently amended claims 210 and 211. Claims 210 and 211 as presently amended

clearly distinguish the genetically-engineered antibodies as defined therein from standard monoclonal antibodies. Accordingly, reconsideration and withdrawal of the rejection of claims 210 and 211 over Gaskin for the same reasons as discussed hereinabove with respect to the rejection of these claims over Bickel, Stern, Walker and Suzuki are respectfully urged.

With respect to claims 212 and 213, the examiner states that Gaskin evidences that the antibodies bind to Aβ 1-28 and that is a long held art accepted principle that an antibody is reactive to the antigenic epitope to which it binds. The examiner further states that because Gaskin teaches that the antibodies bind epitope 1-28 of human Aβ, they would therefore also be suitably obtained thereby. This part of the rejection is respectfully traversed.

Claims 212 and 213 require that the monoclonal antibody be "obtainable using a peptide consisting of residues 1-28 of β-amyloid as an immunogen." Gaskin teaches that the antibodies bind to Aβ 1-28, but that they bind even better to Aβ1-40. The examiner's position is that, because the antibodies bind to Aβ 1-28, they must be obtainable by use of Aβ 1-28 an immunogen. This is essentially taking the position that the fact that the antibody is obtainable using 1-28 as an immunogen would be an inherent characteristic of the antibody. In this regard, however, the examiner's attention is invited to MPEP 2164.05(a)IV "EXAMINER MUST PROVIDE RATIONALE OR

EVIDENCE TENDING TO SHOW INHERENCY," which states in pertinent part:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted) … .

Thus, the feature that the antibodies are obtainable using Aβ 1-28 as an immunogen must necessarily be present in the antibodies of Gaskin in order for such an inherency rejection to be maintained.

Attached hereto is a declaration of Prof. Jonathan M. Gershoni, an expert in the field of antibody:antigen interaction. After review of the Gaskin publication, Prof. Gershoni opined that, while there is a hypothetical scenario in which the Gaskin antibodies would be obtainable using Aβ 1-28 as an immunogen, such a theoretically possible explanation

is not the most likely explanation. Dr. Gershoni explains that the identification of a peptide bound by a given monoclonal antibody does not promise that immunization with that peptide will lead to reproduction of antibodies similar to the original monoclonal antibody. This statement is supported by evidence from the literature that is submitted with the declaration. Thus, for example, mAb 2F5 binds the linear sequence ELDKWAS of HIV gp41, but use of ELDKWAS as an immunogen will not produce an antibody with similar neutralizing activity as that of mAb 2F5.

Prof. Gershoni further states that the inability to reproduce the original antibody is even more likely when the original antibodies are the product of natural events as in Gaskin. In Gaskin it is known that the natural antigen is full length Aβ protein and that the antibodies are the result of rare autoimmune reactions for which a unique cascade of events may be necessary to present the epitope such that it can break tolerance. Prof. Gershoni states that one would not expect that the Aβ 1-28 peptide would be able to reproduce the unique circumstances that the full length protein was able to break tolerance *in vivo* in an autologous situation.

Prof. Gershoni states that the most likely explanations for Gaskin's result of enhanced binding for 1-40 are based on two lines of thought that are basic and common in the field of antibody:epitope interaction, both of which exclude the possibility that 1-28 would be sufficient. In the first scenario, Aβ 1-28 contributes most of the contacts with

the monoclonal antibodies, but additional contacts may exist in residues 29-40. Thus, the antibodies bind residues in residues 1-28 and in 29-40 of Aβ. In such a situation it would be expected that the antibody would bind 1-28, but it would bind 1-40 even more strongly. Prof. Gershoni cites the pepscan of the Lundkvist reference as support for the existence of this scenario. Lundkvist establishes that, while an antibody might bind very well to a peptide containing all of the required residues, it may still bind more weakly to overlapping peptides on either side of the preferred one.

A second scenario would be that residues 29-40 are essential for imposing a unique but critical conformation in residues 1-28, which residues 1-28 could not otherwise assume alone. Prof. Gershoni cites Sgourakis to support that hypothesis. Sgourakis establishes that residues 29-40 of Aβ are likely to be involved in supporting a novel conformation of residues 1-28.

In either of these scenarios an antibody with the properties of the antibodies of Gaskin would not be raised using Aβ 1-28 as an immunogen.

Accordingly, the following, from page 8 of the declaration, are the conclusions of Prof. Gershoni's expert opinion, as supported by the documentary evidence cited in the declaration:

> … I would conclude that it would be highly unlikely to expect that the Aβ 1-28 synthetic peptide would be able to elicit antibodies similar to those reported by Gaskin. Accordingly, I definitely could not

> conclude that, based on the information provided in the Gaskin publication, at least one of the four disclosed antibodies of Gaskin would necessarily be producible using Aβ 1-28 is the immunogen. In my opinion, for the reasons provided above, such a conclusion would be unsupportable.

Accordingly, the extrinsic evidence now of record in this case establishes that the antibodies of Gaskin would not necessarily be obtainable using Aβ 1-28 as an immunogen. There are other more likely scenarios by which these antibodies could not be so raised. Accordingly, the inherency rejection cannot stand. Reconsideration and withdrawal of the rejection of claims 212-213 over Gaskin are therefore also respectfully urged.

Obviousness Rejections

Claims 177, 212 and 213 have been rejected under 35 U.S.C. 103(a), as being obvious over either Bickel or Stern in view of Becker and Anderson. The examiner states that Bickel's and Stern's AMY-33 is a monoclonal antibody that meets the limitations of a genetically-engineered antibody that is obtained from DNA encoding a monoclonal antibody, as claimed. The examiner states that since Becker teaches pharmaceutical formulations containing antibodies having specificity for the β-amyloid peptide, and since the reference teaches that chimeric humanized, veneered, resurfaced or CDR-grafted antibodies, single chain antibodies and human monoclonal antibodies and fragments thereof are preferred for reduction of hyper-immunogenicity *in vivo* when used for

treatment or for detection of amyloid plaque, the reference provides motivation to combine. This rejection is respectfully traversed.

As discussed hereinabove, the Anderson reference has been antedated by the declaration under 37 CFR 1.131 previously submitted and in light of the *Hachiken* case discussed above. Accordingly, the present rejection will be discussed as if it were Bickel or Stern in view of Becker alone as Anderson is not available as a reference.

It is essentially the examiner's position that the artisan would be motivated by Becker to modify the AMY-33 antibody of Bickel or Stern to a human, humanized, or single-chain form for *in vivo* administration, detection and diagnosis of disease or for treatment as taught by Becker. The examiner states that the preferred epitope specificity is provided by the AMY-33 species. However, there is nothing in Becker or in any of the examiner's reasoning that would provide motivation to use AMY-33 therapeutically for any purpose. Unless there is a motivation to use AMY-33 therapeutically, there would be no reason to convert it to a human (and the examiner has not established that it is even possible to convert a murine antibody to a human antibody), humanized or single-chain form for *in vivo* administration.

Becker states that one must select from the universe of anti-Aβ antibodies only those that bind to the β-sheet form of Aβ, but not to the α-coil form. Accordingly, Becker might provide motivation to use the AMY-33 of Bickel or Stern

therapeutically only if there is some reason to believe that the AMY-33 antibody would have the properties that Becker considers to be critical for therapeutic use. If there is no reasonable reason to believe that AMY-33 will necessarily bind to the β-sheet form of Aβ but not to the α-coil form, then Becker would provide no motivation for the use of such an antibody therapeutically. Becker does not provide motivation to use any and all anti-Aβ antibodies therapeutically. He only discusses using anti-Aβ antibodies that have the selective ability to bind to the β-sheet form of Aβ, but not to the α-coil form. Unless there is motivation to use AMY-33 therapeutically, there is no motivation to subject it to genetic engineering.

The examiner states that the requirement to show that AMY-33 has a high level of specificity for β-amyloid in the β-sheet form is not recited in the rejected claims, and thus it is not necessary that the examiner establish that AMY-33 would have these properties. However, the issue is not whether this feature is in the present claims, but whether there is motivation to combine Bickel and Stern with Becker. The only discussion provided by Becker is to therapeutically use an antibody with a high level of specificity for the β-sheet form. Unless there is some reason to believe that AMY-33 has this specificity, there is simply no motivation to use it therapeutically. The fact that Becker teaches that genetic engineering of an anti-Aβ antibody can be done, does not provide motivation to do it to AMY-33.

It would not be obvious-to-try AMY-33 to see if it has the properties desired by Becker because there would be no reasonable expectation that AMY-33 would successfully be shown to have these properties. See *KSR International v. Teleflex Inc.*, 550 US 398, 82 USPQ2d 1385 (2007). *KSR* indicates that the "obvious-to-try" standard only applies when there are a finite number of identified, predictable solutions. Note *KSR*'s analysis of obvious-to-try where it states, 82 USPQ2d at 1390:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp.

This statement of the Supreme Court has recently been analyzed by the Federal Circuit in *Eisai Co. Ltd. v. Dr. Reddy's Laboratories Ltd.*, 87 USPQ2d 1452 (Fed Cir 2008). Citing this portion of *KSR,* the court stated at 1457:

> To the extent an art is unpredictable, as the chemical arts often are, *KSR's* focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.

As AMY-33 is not one of a finite number of identified predictable solutions to the problem posed by Becker, i.e., finding antibodies with a specificity to the β-sheet form of Aβ, it would not have been obvious to try AMY-33 to see if it had the properties desired by Becker.

Accordingly, there is no motivation from any reading of Becker to use AMY-33 therapeutically, as there would be no expectation that it would lead to any desirable results. If there would not be motivation to use AMY-33 therapeutically, there would be no motivation to subject it to genetic engineering. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Claim 177 has been rejected under 35 U.S.C. 103(a) as being obvious over Gaskin in view of Becker and Anderson. The examiner states that Gaskin teaches a monoclonal antibody of the requisite epitope specificity, but which is not a single-chain. The examiner states that Becker and Anderson teach administration of antibodies, including single-chain antibodies. The examiner concludes that the artisan would be motivated by Becker and Anderson to modify the Gaskin antibody with the requisite epitope specificity to single-chain form for *in vivo* administration, detection and diagnosis of disease or for treatment as taught by either Becker or Anderson. The examiner states that it is not necessary that Gaskin teach or suggest that its antibody has the properties disclosed by Becker or Anderson. This rejection is respectfully traversed.

As Anderson is not available as a reference, it need not be discussed. This rejection must fall for the same reasons as discussed above with respect to the rejection of Bickel or Stern in view of Becker. As discussed above, Becker only provides motivation to use an antibody therapeutically, and to genetically-engineer it, if that antibody has the very

special properties of being highly specific to the β-sheet form of Aβ but not binding to the α-coil form. Thus, one of ordinary skill in the art at the time the invention was made would only find motivation to combine Gaskin with Becker if there were good reason to believe that the antibodies of Gaskin had the properties required for therapeutic use as taught by Becker. As there is no reason to believe that the antibodies of Gaskin would have Becker's specificity, there would be no motivation to use the antibodies of Gaskin therapeutically and, therefore, there would be no motivation to convert it to single-chain form. Accordingly, for the same reasons as discussed above with respect to the rejection based on Bickel or Stern in view of Becker, the rejection of Gaskin in view of Becker must also fall. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 177 and 212-213 have been rejected under 35 U.S.C. 103(a) as being obvious over Walker in view of Becker and Anderson. The examiner considers that the artisan would have been motivated by Becker and Anderson to modify the Walker antibody with the requisite epitope specificity to human, humanized or single-chain form for *in vivo* administration, detection, and diagnosis of disease or for treatment, as taught by either Becker or Anderson. This rejection is respectfully traversed.

As Anderson is not available as a reference, it need not be discussed. This rejection must fall for the same reasons as discussed above with respect to the other

obviousness rejections. There would have been no reasonable expectation that the 10D5 antibody of Walker would have the very special properties required by Becker. Accordingly, as there would be no motivation to use the 10D5 antibody therapeutically and therefore no motivation to genetically engineer it, the present invention would not have been obvious in the sense required by 35 U.S.C. 103. Accordingly, reconsideration and withdrawal of this rejection for the same reasons as discussed above with respect to those rejections using Bickel, Stern or Gaskin as the primary references are respectfully urged.

Claims 177 and 212-213 have been rejected under 35 U.S.C. 103(a), as obvious over Suzuki in view of Becker and Anderson. The examiner's reasoning is the same as discussed above with respect to Walker, Stern and Bickel. This rejection is respectfully traversed.

As Anderson is not available as a reference, it need not be discussed. As with the previous obviousness rejections, there is absolutely nothing in Suzuki that would create a reasonable expectation that it could successfully be used for the purpose required by Becker for its antibodies. Accordingly, this rejection must be withdrawn for the same reasons as discussed above with respect to the other obviousness rejections. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Conclusion

It is submitted that all of the claims now present in case clearly define over the references of record and fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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